of neutrophil engraftment, defined as achieving and ANC of 500/μL with 90% donor chimerism by day +42 was 79% (95% CI 69-88%) and platelet engraftment, defined as achieving an untransfused count of >50,000/μL by day 180 was 71% (95% CI 51-74%). The cumulative incidence of Grade II-IV acute GvHD by day +100 was 44% (95% CI 32-56%) and chronic GvHD by 1 year 23% (95% CI 8-27%). The cumulative incidence of overall survival was 80% (95% CI 71-90%) and 72% (95% CI 61-83%) at 180 and 365 days, respectively. Recipient race, favoring Caucasian [p = 0.02], was the only parameter that impacted survival. HLA matching by low or high resolution criteria did not impact survival. Improved growth and cognitive function was seen in patients with Hurler Syndrome and neonates transplanted with Krabbe disease. Patients with presymptomatic ALD and juvenile MLD also did well. Engraftment of donor cells was documented in heart and brain in two patients studied at autopsy. In conclusion, unrelated cord blood (UCB) represents an excellent stem cell source for transplantation therapy for infants and young children with selective inborn errors of metabolism. UCB donors are readily available and cord blood units generally contain more than sufficient cell doses for these younger and smaller patients. Newborn screening for lysosomal and peroxisomal storage diseases would allow for early diagnosis and maximally effective treatment.

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CORD BLOOD TRANSPLANTATION FOR CHILDREN WITH ACUTE LEUKEMIA: AN EUROCORD REGISTRY ANALYSIS

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Unrelated cord blood transplantation has been used to treat patients with malignant and non-malignant hematopoietic disorders for whom a HLA-compatible hematopoietic stem cell donor is not available. The establishment of cord blood banks worldwide, the increased number of cord blood units frozen and the shorter time to find a donor have made possible to use this source of hematopoietic stem cells to treat more than 2 500 patients. The Eurocord registry was established to study the clinical results of cord blood transplantation and to compare the outcomes of unrelated transplants using either cord blood or bone marrow. Briefly, we have found in two distinct retrospective analyses concerning children or adults with acute leukemia given either an unrelated cord blood or bone marrow transplant, that leukemia free-survival and relapse were similar in both types of graft (with adjustment for confounding clinical factors). Cord blood recipients experienced decreased incidence of acute graft-versus-host disease and delayed hematopoietic recovery compared to bone marrow recipients. In order to improve the delayed hematopoietic recovery after cord blood transplantation, certain approaches have been investigated such as ex-vivo expansion of cord blood cells, double cord blood transplantation and reduced intensity conditioning regimen. We have also attempted to establish some guidelines for cord blood donor choice based on cord blood cell dose and number of HLA disparities that have been found to be associated with hematopoietic recovery.

Results of unrelated cord blood transplantation (UCBT) in childhood acute myeloid leukemia: We analyzed 95 children receiving UCBT for AML (20 in CR1, 47 in CR2 and 28 in more advanced stage). Poor prognosis cytogenetic abnormalities were identified in 29 cases. Most patients received a 1 or 2 HLA antigens mismatched transplant. The median number of collected nucleated cells (NC) was 5.2×10^7/kg. Cumulative incidence (CI) of neutrophil recovery was 78 ± 4%, acute graft versus host disease (GvHD) was 35 ± 5% and 100-day transplant-related mortality (TRM) was 20 ± 4%. In multivariable analysis, a collected NC dose higher than 5.2×10^7/kg was associated with a lower 100-day TRM. The 2-year CI of relapse was 29 ± 5% and was associated with disease status. The 2-year LFS was 42 ± 5%, (59 ± 11% in CR1, 50 ± 8% in CR2, and 21 ± 9% for children not in CR). Children with poor prognosis cytogenetic features had similar LFS compared to other patients (44 ± 11% vs 40 ± 8%). In CR2, LFS was not influenced by the length of CR1 (53 ± 11% in CR1 <9.5 months compared to 50 ± 12% in later relapses). We conclude that UCBT is a good therapeutic for children with very poor prognosis AML and who lack an HLA-identical sibling.

Results of unrelated cord blood transplant in children with acute lymphoid leukemia: 195 patients with ALL were analyzed. The median age at diagnosis was 4 years and at transplant 7 years. The median follow-up time was 31 months. 35 patients were transplanted in CR1 (with high risk cytogenetics abnormalities 85%), 85 in CR2, 45 in CR3 and 40 in relapse. 16 patients had received a previous autologous or allogeneic transplant. The median number of nucleated cells infused was 3.8×10^7/kg, and the median CD34+ cell dose was 1.7×10^5/kg. The donor was HLA identical in 21 cases, had 1/6 HLA differences in 80 cases, 2/6 HLA differences in 78 cases and 3/6 HLA differences in 8 cases. Median day to neutrophil engraftment was 29 days, median day to platelet engraftment was 77 days. The cumulative incidence of neutrophil engraftment at 60 days was 85%. It was dependent on the number of nucleated cells infused. The incidence of GVH was low with 63% grade 0-1, 16% grade II, 12% grade III and 9% grade IV. Estimate incidence of chronic GVH was 34%. Two-year transplant related mortality was 39% in patients transplanted in CR and 58% in patients transplanted in relapse. In multivariate analysis, 3 factors were associated with an increasing probability of non-leukemic death: advanced disease (p = 0.04), previous transplant (p = 0.03) and centers performing less than 10 cord blood transplants (p = 0.0004). The cumulative incidence of relapse was 28%. The predictive factors for relapse were: use of methotrexate for prevention of GVH (p = 0.02), longer time between diagnosis and CBT (p = 0.009), absence of acute GVH (p = 0.002). Two-year DFS was 36% in patients transplanted in CR and 15% in patients transplanted in remission. Predictive factors increasing the probability of disease free survival were: remission status of the disease at transplant (p = 0.0006), previous transplant (p = 0.0001), centers performing less than 10 CBT (p = 0.01). In conclusion, these results show that unrelated HLA mismatched cord blood transplant can cure a proportion of children with ALL who do not have a bone marrow donor. The number of cells infused is a major factor associated with hematopoietic recovery. The presence of GVH is associated with a decreased risk of relapse. The center effect is an important factor for survival probably in relation to the selection of the patients (time to transplant) and donor choice (number of cells infused).

Results of unrelated cord blood transplants compared to unrelated bone marrow transplants in children with acute leukemia: A multicenter retrospective analysis comparing the outcome of unrelated cord blood transplant to unrelated bone marrow transplants in children with acute leukemia was performed by Eurocord and EBMT. Five hundred and fifteen children with acute leukemia receiving either an unrelated cord blood transplant (UCBT, n = 99) or an unrelated BMT (n = 416) were analyzed. Recipients of UCB were younger and had more pre-transplant adverse disease factors. Most of the bone marrow donors were HLA matched or had a maximum of 1 HLA difference while most of the cord blood donors had 2 to 3 HLA differences. The median number of nucleated cells infused was 4×10^8/kg in unrelated BMT and 0.38×10^8/kg in unrelated UCBT. In unrelated BMT, 262 children received an unmanipulated BMT and 180 a T-cell depleted BMT using Campath-1M as the most frequent means of T-cell depletion. The median follow-up was 29 months. During the first 100 days after transplant, while unmanipulated and T-cell depleted BMT did not differ in hematopoietic recovery and treatment related mortality, the main findings that emerged from these retrospective adjusted comparisons were the poor results of UCBT concerning neutrophil and platelet recoveries and early transplant related mortality. In contrast UCBT and T-cell depleted BMT gave less acute GVHD than the unmanipulated BMT group. Finally the unmanipulated BMT and the UCBT groups had less leukemic relapse than the T-cell depleted group. Considering the long-term outcome, the unmanipulated BMT group had more chronic GVHD than the T-cell depleted BMT and the UCBT groups. Furthermore, while outcome in the 3 groups was comparable in terms of long term relapse, mortality after day 100 was increased in the T-cell depleted BMT group mostly because of the occurrence during the first 100 days post-BMT of early relapse and infections. In summary, the main differences in adjusted outcomes

between the three transplant groups appeared in the first 100 days post transplant but without giving advantage to any group. Indeed, the delay of engraftment and increased treatment-related mortality observed after UCBT must be balanced with the higher risk of acute GVHD after unmanipulated BMT and with the higher risk of relapse after T-cell depleted BMT. In contrast, after day 100 posttransplant, the 3 groups achieved similar results in terms of relapse but chronic GVHD and death occurred more frequently with unmanipulated BMT and T-cell depleted BMT respectively. These results justify the simultaneous search for unrelated cord blood and unrelated bone marrow donors for children with acute leukemia. The decision to perform cord blood transplants will be based on the cell content of the graft, the number of HLA disparities and the urgency of the transplant.

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UNRELATED CORD BLOOD TRANSPLANTATION FOR TRANSFUSION-DEPENDENT THALASSEMIA IN CHILDREN

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Hematopoietic stem cell transplantation is currently the only curative therapy for transfusion-dependent thalassemia. However, approximately 30% of patients have unaffected HLA-identical siblings to serve as donors. We investigated the feasibility of unrelated cord blood transplantation (CBT) as a potential strategy for augmenting the pool of acceptable donors. Between October 2003 and December 2004, 9 children with β-thalassemia major received CBT with at least 2.5×10^7/kg TNC from unrelated donors (0-2 of 6 HLA antigens were mismatched) and were then evaluated for engraftment, adverse effects, and treatment outcome. Conditioning consisted of busulfan, cyclophosphamide, and antithymocyte globulin, and GVHD prophylaxis of cyclosporine and methylprednisolone. Median age was 3.7 years (range, 2.3-11.4 years). One patient died of penicillin-resistant *S. mitis* sepsis at day +8 prior to the "expected" time to respond. Eight of 9 patients were alive at median follow-up of 254 days after transplantation, with complete donor chimerism and transfusion independence. The median times to neutrophil engraftment, RBC transfusion independence, and platelet engraftment were 13, 34, and 45 days after transplantation, respectively. The patients showed grade I-III acute GVHD. No extensive chronic GVHD had developed at the latest contact. The medical costs per-patient with CBT in Taiwan is estimated to be approximately US$40,000 plus the cost of the cord blood unit. In summary, our results suggest that unrelated CBT is an alternative treatment for patients with transfusion-dependent thalassemia lacking an HLA-matched sibling bone marrow donor, and it is clearly cost-effective when compared to conventional treatment with blood transfusions and iron chelation therapy.

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OUTCOMES OF UNRELATED CORD BLOOD TRANSPLANTS AND ALLOGENEIC RELATED HEMATOPOIETIC STEM CELL TRANSPLANTS IN CHILDREN WITH HIGH-RISK ACUTE LYMPHOCYTIC LEUKEMIA

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Background: HSCT is commonly used for pediatric ALL patients (pts) with early relapse or other high-risk features. Given lack of matched-sibling donors and multiple advantages of UCB as stem cell source (less GVHD, rapid availability), we compared outcomes of pediatric ALL pts that underwent HSCT with UCB (4-5/6 HLA) or matched-sibling transplant (6/6 HLA).

Methods: Pts included: ALL CR2 pts who relapsed <36 mos from diagnosis and ALL CR1 pts with ≥1 high-risk feature (unfavorable karyotype, poor response to induction, age <1 yr, WBC >100,000 at diagnosis). 25% of CR1 pts in both groups had ≥2 high-risk features. Cytoreduction (same in both groups): Pts received TBI 150 cGy × 8 (d −10 to −7); VP-16 1 g/m^2/day (d −6 to −5); cyclophosphamide 60 mg/kg/day (d −4 to −2). GVHD prophylaxis: CSA, short-course MTX, and ATG d +1, +3, +5, +7 (for UCB). Grafts were not T-cell depleted.

Results: There were 23 matched-sibling (20 BM/3 PBSC) and 26 UCB recipients. Both groups had equivalent high-risk factors. Engraftment took longer in UCB recipients. TRM and GVHD were equal in both groups. 3 yr EFS is 60% in both groups. Age, gender, degree of HLA-matching for UCB, acute/chronic GVHD did not affect EFS.

Conclusions: In pediatric pts with high-risk ALL in need of HSCT, outcome of matched-sibling HSCT and UCB transplant is equivalent with regards to TRM, GVHD, and EFS. UCB should be considered a standard stem cell source to use in this group when a matched sibling is not available.

Table 1.

	Matched-sibling (n = 23)	UCB (n = 26)	p
Age diagnosis (yrs)*	2.5 (0.3-15.4)	3.9 (0.3-11.9)	0.63
Status at HSCT (CR1)	11 (47.8%)	10 (38.5%)	0.34
Age <1 yr	7 (30.4%)	6 (23.1%)	0.56
Karyotype (unfavorable)	8 (34.8%)	11 (42.3%)	0.79
Neutrophil recovery (d)*	16 (13-21)	29 (21-35)	<0.001
Platelet recovery (d)*	24 (17-35)	51 (32-59)	0.011
100d TRM†	3 [13% (3-34)]	5 [19% (7-39)]	0.71
aGVHD (2-4)†	5 [22% (7-44)]	5 [19% (7-39)]	0.83
CGVHD (in at risk)†	8 [40% (19-64)]	7 [33% (15-57)]	0.66
Relapse at 3 yrs†	5 [22% (7-44)]	4 [15% (4-35)]	0.72
3 yr EFS†	60% (40-80)	61% (42-80)	0.72

*Median (range); †% (95% CI).

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TOTAL BODY IRRADIATION, FLUDARABINE, MELPHALAN AND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ADVANCED PEDIATRIC HEMATOLOGIC MALIGNANCIES

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The Fludarabine (F)-Melphalan (M) reduced-intensity preparative regimen has been successfully used in adults for allogeneic hematopoietic stem cell transplant (HSCT). We evaluated the efficacy and toxicity of adding 9 Gy of total body irradiation (TBI), in three single daily fractions of 3 Gy, to the reduced intensity regimen of fludarabine 30 mg/m^2 i.v. × 4 days and melphalan 140 mg/m^2 i.v. × 1 day in advanced pediatric hematologic malignancies. GVHD prophylaxis consisted of tacrolimus and mini-methotrexate. No anti-thymocyte globulin was used. Twenty-two acute lymphoblastic leukemia (ALL), 6 acute myeloid leukemia (AML), and 1 anaplastic large-cell lymphoma patients were transplanted. Thirteen of these were beyond second remission, and five had prior HSCT. Twenty-one donors were unrelated: 1-2 antigen mismatched cord blood (CB) for 19 patients, bone marrow in one and peripheral blood stem cells (PBSC) in one. Three of the 8 related donors were genotypically disparate. Oral mucositis and diarrhea were the most common side effects seen. Twenty-seven patients achieved neutrophil engraftment at a median of 16 days (range 11-35), and 23 had platelet engraftment (median 42 days, range 14-200). One patient had primary graft failure. Seven patients (all with ALL) died of non-relapse causes in the first 100 days. Six of 27 evaluable patients developed grade III-IV acute GVHD and three chronic GVHD. Nine patients (7 with ALL) relapsed at a median of 8 months post-transplant (range 2-54). With a median follow-up of 55 (range 25-88) months, 7 of 22 ALL, 5 of 6 AML, 1 of 1 lymphoma patients are alive and in remission. This includes eight of the 19 CBT recipients. The regimen of TBI, F and M allows the engraftment of allogeneic HSC (including mismatched unrelated